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EDITORIAL

The End of the Digoxin Era?

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ABSTRACT

Digoxin is one of the oldest of cardiovascular drugs which is still frequently used, both in patients with atrial fibrillation (AF) and patients with heart failure with or without AF. The use of digoxin preceded the era of evidence based medicine. However, over the recent past, there has been growing evidence disputing and challenging the safety and efficacy of digoxin, while evidence has accumulated that a plethora of other therapies for both heart failure and atrial tachyarrhythmias has proven more effective and safe. Nevertheless, digoxin still retains its role, albeit limited, in the current era, but most recent evidence has cast significant doubts about its safety. Thus, its role remains controversial and the drug should be reserved for specific patients and clinical scenarios, with careful monitoring of its serum concentration due to its narrow therapeutic and toxic ranges, maintaining it <0.8 ng/mL, with additional monitoring of serum electrolytes and renal function to avoid potential confounders that may enhance the proarrhythmic risk and susceptibility to digoxin toxicity.

Key Words: digitalis; digoxin; atrial fibrillation; heart failure; mortality; proarrhythmia; digoxin toxicity

Abbreviations

AF = atrial fibrillation; CRT-D = cardiac resynchronization therapy-defibrillator; DIG = Digitalis Investigation Group; HR = hazard ratio; ICD = implantable cardioverter defibrillator; NYHA = New York Heart Association; TTR = time in therapeutic range; VF = ventricular fibrillation; VT = ventricular tachycardia

INTRODUCTION

Digoxin has been included in our therapeutic armamentarium for heart failure and atrial tachyarrhythmias for over 200 years following Withering's milestone work suggesting the therapeutic value of the plant foxglove in his 1785 classic monograph.[1] However, there has never been any evidence of a survival benefit,[2] while recently, evidence has accumulated suggestive of a harmful effect.[3-6] While in atrial fibrillation (AF) digoxin may have a role in the control of ventricular rate when added to beta-blockers and calcium antagonists, which may have to be revisited in light of this recent evidence, digoxin for heart failure may no longer be a supportable option in view of all the data that have been accumulated todate.

Since the results of the Digitalis Investigation Group (DIG) trial,[2] indicating that digoxin does not reduce overall mortality, but it may reduce the rate of hospitalization both overall and for worsening heart failure, over long-term follow-up (3 years),[2] but also during the first 30 days,[7] the role of digoxin was further limited in the management of chronic heart failure, especially when more beneficial therapies for patients with heart failure were effected. Digoxin has also been employed in patients with AF to control the ventricular rate by enhancing vagal tone and thus decreasing conduction over the atrioventricular node. However, these effects are relevant only at rest and not during physical activity, since digoxin has limited utility in the setting of increased sympathetic activity. Thus, for more effective rate control the drug should be used in combination with a beta-blocker or a calcium antagonist. Furthermore, digoxin's beneficial effects are offset by its potential deleterious effects, arrhythmogenic potential, narrow therapeutic window and risk for serious drug interactions.

Indeed, recent meta-analyses and reviews of non-randomized studies have suggested that digoxin use is associated with an increased risk of all-cause mortality in patients who have both heart failure and AF, even after adjustment for confounding variables.

Atrial Fibrillation

According with a US retrospective study (TREAT-AF: The Retrospective Evaluation and Assessment of Therapies in AF),[6] among 122,465 male patients (mean age 72 years) with newly diagnosed nonvalvular AF with 353,168 person-years of follow-up, cumulative mortality rates were higher for 28,679 (23.4%) digoxin-treated patients than for untreated patients (95 vs 67 per 1,000 person-years; $p < 0.001$). Digoxin use was independently associated with mortality after multivariate adjustment (hazard ratio -HR: 1.26, $p < 0.001$) and propensity matching (HR: 1.21, $p < 0.001$), even after adjustment for drug adherence. The authors concluded that digoxin was associated with increased risk of death in patients with newly diagnosed AF, independent of drug adherence, kidney function, cardiovascular comorbidities, and concomitant therapies.

Another US retrospective cohort study, the AnTicoagulation and Risk factors In Atrial fibrillation-Cardiovascular Research Network (ATRIA-CVRN) study,[8] comprising 14,787 age- and gender-matched adults with incident AF and no previous heart failure or digoxin use, indicated that during a median 1.17 years of follow-up, digoxin use was associated with higher rates of death (8.3 vs 4.9 per 100 person-years; $P<0.001$) and hospitalization (60.1 vs 37.2 per 100 person-years; $P<0.001$); digoxin use conferred a 71% higher risk of death (hazard ratio, 1.71) and a 63% higher risk of hospitalization (hazard ratio, 1.63). The authors concluded that in adults with AF, digoxin use was independently associated with higher risks of death and hospitalization and thus it should be used with caution in the management of AF.

A recent study investigated whether AF patients receiving rate control drugs (N = 101,243) had a better prognosis compared to those without rate-control treatment (N = 168,678).[9] Rate controlled agents included beta-blockers (n = 43,879), calcium channel blockers (n = 18,466) and digoxin (n = 38,898). During a follow-up of 4.9±3.7 years, mortality occurred in 88,263 patients (32.7%). The risk of mortality was lower in patients receiving beta-blockers (hazard ratio - HR = 0.76) and calcium channel blockers (HR = 0.93) compared to those who did not receive rate-control agents. On the contrary, the digoxin group had a higher risk of mortality with a HR of 1.12. The authors concluded that in this nationwide AF cohort, rate-control treatments with beta-blockers or calcium channel blockers reduced mortality, with beta-blockers conferring the largest risk reduction, while digoxin use was associated with greater mortality.

Even in a "real world" cohort of 815 AF patients on good anticoagulation treatment (time in therapeutic range - TTR ~65%), the use of digoxin (n=171) was associated with an increased risk of total mortality over a median follow-up of 33.2 months.[10] Indeed, multivariable analysis showed that digoxin was associated with total mortality (hazard ratio -HR: 2.224, $p < 0.001$) and cardiovascular death (HR: 4.686, $p < 0.001$).

Heart Failure

The Digitalis Investigation Group (DIG) trial was the pivotal trial showing that digoxin reduces the risk for hospitalization but not mortality among 6,800 stable patients (mean age 65 years) with heart failure (NYHA functional class II or III) and a left ventricular ejection fraction $\leq$45% who were in sinus rhythm.[2] The DIG ancillary trial had a similar design and was conducted in parallel to the main study but included patients with ejection fractions >45% ("diastolic" heart failure or heart failure with preserved ejection fraction).[11] The ancillary trial comprised 988 patients and found no effects on all-cause, cardiovascular, or heart failure mortality or on all-cause or cardiovascular hospitalizations.

Post-hoc analyses of the DIG trial and other trial databases prompted the revised recommendation suggesting a much lower (0.5 to 0.8 ng/ml) than previously considered therapeutic serum digoxin level (1.0 to 2.0 ng/ml) in order to obtain the favorable effects of digoxin and avoid its deleterious consequences on long-term survival.[12] Unfortunately, despite these recommendations

for lower dosing and the accumulation of worrisome data about the long-term use of digoxin, digoxin toxicity is not yet declining according with the US data, accounting for an estimated 1% of emergency room visits for all adverse drug events among patients ≥40 years, rising to ~3% of emergency room visits and ~6% of hospitalizations for all adverse drug events among patients ≥85 years.[13]

Recently, in the cohort of 1820 patients with mild heart failure (NYHA class I and II), prolonged QRS duration (≥ 130 ms), and reduced left ventricular ejection fraction (≤30%) enrolled in the Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT) trial,[14] digoxin therapy was not associated with an increased or decreased risk of heart failure/death (hazard ratio -HR 1.07), heart failure alone (HR 1.1), or death alone (HR 0.93). However, digoxin was associated with a significant 41% increased risk of ventricular tachycardia / ventricular fibrillation (VT/VF) (HR 1.41; P = 0.002), which was driven by a significantly increased risk of VT/VF with heart rate ≥200 bpm (HR 1.65; P ≤ 0.001), whereas no increased risk of VT/VF with heart rate <200 bpm was evident (HR 1.20; P = 0.19). The authors concluded that the use of digoxin in patients with mild heart failure implanted with an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) device was not associated with reductions in heart failure/death events; however, digoxin therapy was associated with an increased risk of high-rate VT/VF.

Atrial Fibrillation and Heart Failure

A meta-analysis of 10 studies (4 registries, 4 single-center cohort studies and 2 post-hoc analyses of randomized controlled trials) comprising 76,100 patients with AF and heart failure indicated that over a follow-up period of 0.8-4.3 years, digoxin was associated with an increased risk of all-cause mortality (relative risk - RR: 1.15, p=0.005).[3] Subgroup analysis revealed that the pooled relative risk of all-cause mortality with the use of digoxin was similar between 8 observational studies (n = 66,174, RR: 1.11) and 2 post-hoc analyses of randomized controlled trials (n = 9926, RR: 1.27, interaction p=0.11). The authors concluded that digoxin use is associated with an increased risk of all-cause mortality in patients who have both heart failure and AF, even after adjustment for confounding variables.

A meta-analysis of 11 observational studies, examining the relation between digoxin and all-cause mortality in 318,191 patients with AF, indicated that over a mean of 2.8 years, digoxin use was associated with a 21% increased risk for mortality (hazard ratio 1.21).[15] Importantly, the use of digoxin was associated with an increase in mortality in patients with and those without heart failure.

Use and outcomes of digoxin were examined in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial.[16] Among 14,171 AF patients (history of heart failure 56%-73%; digoxin use at baseline 37%), digoxin was associated with increased all-cause mortality (5.41 *vs* 4.30 events per 100 patients-years; hazard ratio-HR 1·17; p=0.0093), vascular death (3.55 *vs* 2.69 per 100 patient-years; HR 1·19; p=0.0201), and sudden death (1.68 *vs* 1.12 events per 100 patient-years; HR 1·36; p=0·0076). The authors concluded that digoxin treatment was associated with a significant increase in all-cause mortality, vascular death, and sudden death in patients with AF, noting that this increased cardiovascular hazard was observed in those with and without heart failure. The authors also indicate that other drugs, such as β blockers and non-dihydropyridine calcium channel antagonists, should be employed for rate control in patients with AF, whilst digoxin treatment should not be deemed a first-line treatment and should be used with caution in patients with AF with or without heart failure. They point out that further randomized studies are needed to define the optimum rate control therapies, including the role of digoxin.

Another meta-analysis of 19 reports (9 comprising AF patients, 7 heart failure patients, and 3 with both clinical conditions) indicated that among 326,426 patients, digoxin use was associated with an increased relative risk of all-cause mortality (hazard ratio - HR 1.21, P < 0.01).[5] In the subgroup of reports comprising 235,047 AF patients, digoxin was associated with a 29% increased mortality risk (HR 1.29) compared with subjects not receiving the drug. Among 91,379 heart failure patients, digoxin-associated mortality risk increased by 14% (HR 1.14). The authors concluded that digoxin use is associated with an increased mortality risk, particularly among patients suffering from AF.

The results of a more recent meta-analysis contrasted those of observational studies. This meta-analysis comprised 52 studies and 621,845 patients, whereby digoxin users were 2.4 years older than control, with lower ejection fraction (33% vs 42%), more diabetes, and greater use of diuretics and anti-arrhythmic drugs.[17] Compared with control, the pooled risk ratio for death with digoxin was 1.76 in unadjusted analyses, 1.61 in adjusted analyses, 1.18 in propensity matched studies, and 0.99 in randomized controlled trials. Baseline differences between treatment groups appeared to have a significant impact on mortality associated with digoxin, including markers of heart failure severity such as use of diuretics (P=0.004). Studies with better methods and lower probability of bias

were more likely to report a neutral association of digoxin with mortality (P<0.001). Across all study types, digoxin led to a small but significant reduction in all cause hospital admission (risk ratio 0.92; P<0.001; n=29,525). The authors concluded that digoxin is associated with a neutral effect on mortality in randomised trials and a lower rate of admissions to hospital across all study types (there were 7 randomized trials included in the analysis conducted in 8,406 heart failure patients).

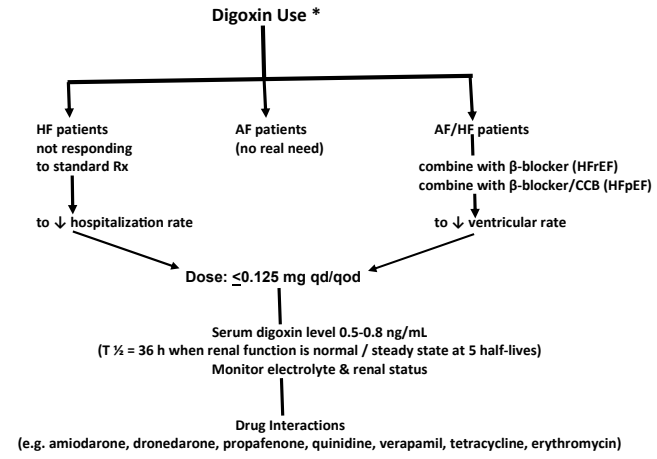
Furthermore, a recent analysis of data from the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) study, among 9,619 patients with AF and serial follow-up every 6 months for up to 3 years, refuted the dismal results of prior reviews and meta-analyses, albeit only for patients with heart failure.[18] In this cohort, 2,267 (23.6%) patients received digoxin at study enrollment, 681 (7.1%) were started on digoxin during follow-up, and 6,671 (69.4%) never received digoxin. Digoxin use at registry enrollment was not associated with subsequent onset of symptoms, hospitalization, or mortality (hazard ratio - HR for death: 1.04 in heart failure patients; HR: 1.22 in patients without heart failure). Incident digoxin use during follow-up was not associated with subsequent death in patients with heart failure (HR: 1.05), but was associated with subsequent death in those without heart failure (HR: 1.99). The authors concluded that digoxin use in registry patients with AF had a neutral association with outcomes under most circumstances, but digoxin was associated with subsequent death in those without heart failure (HR: ~2.0).

Similarly, a recent survey of a prospective, multinational, observational registry of 1962 patients with AF, aged 56 ± 16 years, 36% having a digoxin prescription, and 27% having heart failure, indicated that digoxin therapy was associated with significantly higher mortality in those without heart failure at 6 months (8.7% vs 3.7%; odds ratio - OR, 5.07; P <0.001) and 12 months (12.3% vs 6.0%; OR, 4.22; P < 0.001) but not in those with heart failure (6 months: 18.6% vs 14.7%; OR, 1.62; P = NS and 12 months: 25.4% vs 22.4%; OR, 1.37; P = NS).[19] The authors concluded that in patients with AF and heart failure, digoxin did not offer any survival benefit, while in those without heart failure, digoxin therapy was associated with significantly higher long-term mortality.

Conclusion and Perspective

There appears to be convincing evidence accumulated todate suggesting that digoxin does not prolong survival in heart failure and/or AF patients, while there may be a significant risk of increased cardiovascular mortality in these patients. The data from recent reviews and meta-analyses, admittedly mostly from observational studies, are worrisome and should be taken into serious consideration, especially in the current era, when we have much better and safer alternative therapies for both heart failure and AF. It may not possible to have in the future a randomized controlled trial that may be able to shed further light into this matter, while the results from other meta-analyses refuting, albeit not entirely, the dismal outcome of digoxin use suggested by the majority of prior reviews and meta-analyses of observational data, do not appear to provide any convincing answers that would alleviate one's fears for the potential perilous effects of digoxin.

Thus, it is possible that we are indeed approaching the end of the digoxin era, saving it for now for only specific circumstances, such as patients with heart failure who are not responding well to standard therapies in hope of reducing their hospitalization rate, and patients with both heart failure and AF who cannot tolerate or do not respond to other available rate controlling agents. Even in such clinical conditions of last resort, one has to consider using the lowest possible dose of digoxin while maintaining its serum levels <0.8 ng/mL,[20] with additional monitoring of serum electrolytes and renal function to avoid potential confounders that may enhance the proarrhythmic risk and susceptibility to digoxin toxicity (**Fig**. 1).



* Avoid or extreme caution (much lower doses) in the elderly (≥75-80 years) & patients with renal insufficiency (GFR ≤ 45-60 ml/min) / Digoxin toxicity: correct hyperkalemia, hypokalemia, and hypomagnesemia; correction of electrolyte imbalances may reverse dysrhythmias / ***Digoxin immune Fab*** is extremely effective in the treatment of moderate to severe digoxin toxicity

Figure 1. **A suggested algorithm for selective use of digoxin, if at all**. With regards to digoxin toxicity, physicians should be alert and vigilant to discern between digoxin effect/ no toxicity (i.e., scooped ST-segment or ST-sagging), early toxicity (e.g. atrial or ventricular ectopy, bradyarrhythmia), moderate toxicity (i.e., ventricular arrhythmias, junctional rhythm), or severe life-threatening toxicity (i.e., complete or high-degree AV block, ventricular tachyarrhythmias and hyperkalemia).[12] AF = atrial fibrillation; CCB = calcium channel blocker; GFR = glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; qd = once daily; qod = every other day; Rx = treatment.

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